REMARKS/ARGUMENTS

Claims 10, 19-36, 41 and 42 were previously withdrawn from consideration as being drawn to a non-elected invention and species. Claims 37, 39 and 40 were previously canceled and claims 43 - 45 were previously presented. Claims 1, 3, 4, 17 and 18 were previously amended.

Applicants wish to bring previously presented (10/13/2005 response) claim 45 to the Examiner's attention. This claim appears to have been inadvertently left out of the January 11, 2006 and September 21, 2006 Office Actions.

35 USC 103(a) Rejections

Claims 1-9, 12-18 and 38 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US2003/0072754), Kirk et al. (US2002/0119150), Storb et al. (Blood 94: 2523-2529) and Heeman et al. (Transplant Immunology 4: 64-67, 1996). Applicants respectfully disagree.

The examples found in all of the references cited above report results of studying one agent (anti-CD154 only in Kenyon et al) or combinations utilizing CTLA4Ig and one other agent (CTLA4Ig + MR1 or cyclosporine in Larsen et al.; CTLA4Ig + 5c8 in Kirk et al.; CTLA4Ig + MMF in Storb et al.; CTLA4Ig + LFA-1 in Blazer et al.) in the treatment of transplant rejection. None of the references report data of studies utilizing more than two agents.

The Applicants and the cited art demonstrate that the inhibition of immune responses resulting from the blockade of the CD28/CTLA4/B7 and CD40/CD154, or CD28/CTLA4/B7 and blockers of adhesion molecule-mediated interaction pathway is potent. However, applicants further demonstrate that the inhibition of immune responses resulting from these pathways may be incomplete in some cases. This is demonstrated in Example 1 of the instant application where the inhibition of some of the double pathway treatments do not lead to long-term graft survival. Example 1 also demonstrates that in such cases the use of the three agents as claimed surprisingly is more effective than the double therapy described in the cited art. Only where the inhibition of the cell-mediated immune response is already complete by using the combination of two agents, is the addition of a third agent not appear to provide an additional benefit (see Example 2 of the instant specification)

The teachings of newly cited Storb et al. and Heeman et al. do not provide the missing motivation to combine a third agent to a successful double pathway therapy described in the art. In fact, Storb et al. only reinforces the double therapy pathway described in Blazer et al., Kirk et al., Keynon et al. and Larsen et al. If Blazer is considered in view of Larsen, Kirk, Kenyon, and Storb and the basic principles set forth in Strom et al. and Heeman, at best, the skilled person would consider the use of MMF described by Strom in Table 36.1 and Heeman in combination with a double therapy pathway described in Blazer, Kirk, Kenyon, Larsen and Storb. There would be no motivation to combine an agent that blocks the CD28/CTLA4/B7 pathway with and an agent that blocks the gp39/DC40 pathway and an agent that inhibits adhesion of the T cell, with or without the standard of therapy immunosuppressants especially since all of the reported data in the art show superior results from the various double therapies.

In view of the lack of evidence showing the claimed invention is obvious in view of the cited references, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 12-18 and 38, under 35 USC 103(a).

Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150) Storb et al. (Blood 94: 2523-2529) and Heeman et al. (Transplant Immunology 4: 64-67, 1996) as applied to claims 1-9, 12-18 and 38 above and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

Since Blazer et al., in view of Larsen et al., Strom et al., Kenyon et al., Kirk et al., Storb et al. and Heeman et al. do not render obvious the claimed methods for the reasons discussed above, the fact that reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without the standard of practice immunosuppression agents described by Strom.

Accordingly, the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 6, 8 and 11, under 35 USC 103(a).

Claims 6 and 43-44 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150), Storb et al. (Blood 94: 2523-2529) and Heeman et al. (Transplant Immunology 4: 64-67, 1996) as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US2003/0219863).

Since Blazer et al., in view of Larsen et al., Strom et al., Kenyon et al., Kirk et al., Storb et al. and Heeman et al. do not render obvious the claimed methods for the reasons discussed above, the substitution of L104EA29YIg for CTLA4Ig in the double combination therapy taught by Blazer et al. does not provide the motivation to one skilled in the art to combine the three claimed agents with or without the standard of practice immunosuppression agents described by Strom. The expectation would be that a double combination including L104EA29YIg would be more effective, due to the higher binding avidity of L104EA29YIg compared to CTLA4Ig, with the benefit of less potential for toxicity because of anticipated decreases in dosages, for example.

Applicants respectfully request the Examiner to reconsider and withdraw the above rejections. The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment. The Examiner is invited to contact the undersigned if there are any questions relating to the prosecution of this application.

Respectfully submitted,

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